PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Streptococcal pharyngitis in children: a meta-analysis of clinical decision rules and their clinical variables
AUTHORS	Dubos, Francois; Le Marechal, Flore; Martinot, Alain; Alain, Duhamel; Pruvost, Isabelle

VERSION 1 - REVIEW

REVIEWER	Cohen, Robert CHI Cretei, Pediatrics No conflict of interests
REVIEW RETURNED	26-Sep-2012

RESULTS & CONCLUSIONS	With the results observed, we can draw conclusions completely opposite of the authors. So that, various passages of the article need to be re-written to modulate the authors' conclusions.
GENERAL COMMENTS	This study is interesting, methodologically well conducted and well written. However, with the results observed, we can draw conclusions completely opposite of the authors. So that, various passages of the article need to be re-written to modulate the authors' conclusions. Page 2 key message 2 « Some clinical decision rules are performing as well as some rapid diagnostic test to exclude GAS pharyngitis in children » It is not true: the clinical decision rules perform as well rapid antigen test only for sensitivity and LR- not for specificity ant LR+ For example, the CDR of Joachim the Sp is of 35% (95% for rapid antigen test) and the LR+ is of 1.4 (10 to 20 for rapid antigen test) Recent European and US guidelines do no recommend the use of clinical rules for the management of pharyngitis in children Strength and limitations, Second bullet point « A decision rule that performed as well as most rapid diagnostic tests was identified, but has not been validated until now » Same remark, it is not true for sensitivity and LR+ I suggest « A decision rule that performed as well as most rapid diagnostic tests in term of sensitivity and LHR - was identified, but has not been validated until now » Page 3 Abstract Objective I suggest a modification « To identify the best clinical decision rules (CDRs) for diagnosing group A

	streptococcal (GAS) pharyngitis in children. A combination of symptoms could help clinicians to predict which cases of pharyngitis in children might be GAS infections. » Conclusion « The rule of Joachim et al. could be useful for clinicians who are reluctant to use rapid diagnostic tests and should allow them avoid antibiotic treatment for children who do not have GAS pharyngitis. I think that it is not true, because very few proportion of patient (less than 30%) had had score sufficiently low to allow to not using rapid antigen test or culture

REVIEWER	Dr Carole Cummins Senior Lecturer School of Health and Population Sciences University of Birmingham Edgbaston Birmingham United Kingdom B15 2TH I have no competing interests.
REVIEW RETURNED	27-Sep-2012

THE STUDY	I reviewed an earlier draft of this article and some of my previous points have been addressed. I said in my previous review however that the authors should make it clear that not all guidelines mandatory rapid tests, and although the authors have cited an article that makes this point, it would be worth stating that rapid tests are not recommented practice in all settings internationally, as this implies that the purpose and use to which a decision rule is put may vary. In some settings it would be used to improve diagnosis, but elsewhere might be used to reduce or replace tests. Authors could consider citing the guidelines as well as the review article. While this is perhaps not necessary for publication, it would ensure that differences in practice internationally are made clear. My main outstanding criticism however is that I had previously suggested that databases searched using the OVID platform and via INIST should be specified or the search strategy would be incomplete and unevaluable by the reader. This has not been addressed and is an important point as it influences the assessable quality of what otherwise appears to be a high quality systematic review. It also means that updating would be difficult should anyone wish to do this. For example, was Ebase searched or the Science Citation Index? This really should be clear and would improve a useful paper considerably from the systematic review aspect. Search dates should also be added. Also on review methods: -A flowchart of citations might be expected in the supplementary material. - Ideally text as well as MESH terms would have been used.

	There's a typo - avec instead of have.
RESULTS & CONCLUSIONS	Results are credible as long as more information on the databases searched is provided.
REPORTING & ETHICS	A flow chart would be desirable.

VERSION 1 – AUTHOR RESPONSE

Reviewers' comments
Reviewer 1:
Robert Cohen
CHI Creteil, Pediatrics
Conflict of Interest None

This study is interesting, methodologically well conducted and well written. However, with the results observed, we can draw conclusions completely opposite of the authors. So that, various passages of the article need to be written to modulate the authors' conclusions.
Answer: It has been performed as recommended by the reviewer in the article summary, in the Abstract and in the conclusion.

Page 2 key message 2 « Some clinical decision rules are performing as well as some rapid diagnostic test to exclude GAS pharyngitis in children » It is not true: the clinical decision rules perform as well rapid antigen test only for sensitivity and LR- not for specificity ant LR+. For example, the CDR of Joachim the Sp is of 35% (95% for rapid antigen test) and the LR+ is of 1.4 (10 to 20 for rapid antigen test). Recent European and US guidelines do no recommend the use of clinical rules for the management of pharyngitis in children.
Answer: We completely agree with the reviewer that LR+ of CDRs for pharyngitis is of poor interest. We also agree that recent US guidelines do not recommend the use of clinical rules for the management of pharyngitis in children. However, still a lot of unnecessary antibiotics are prescribed in this situation despite recommendations. Moreover, as mentioned by the other reviewer, rapid diagnostic tests are not recommended everywhere. For these reasons, the use of clinical rules to RULE OUT (i.e., low LR-) may be useful. A modification has been done to be more precise (p2, Key messages, 2nd bullet): "Some clinical decision rules are performing as well as some rapid diagnostic test to exclude GAS pharyngitis in children, but are not performing enough for the positive diagnosis of GAS pharyngitis."

Strength and limitations, Second bullet point « A decision rule that performed as well as most rapid diagnostic tests was identified, but has not been validated until now » Same remark, it is not true for sensitivity and LR+ I suggest « A decision rule that performed as well as most rapid diagnostic tests in term of sensitivity and LHR - was identified, but has not been validated until now »
Answer: A modification has been done to be more precise about the ability of the decision rule to "rule out" the diagnosis and not "to rule in" (p2, Strength and limitations, 2nd bullet): "A decision rule that performed as well as most rapid diagnostic tests to rule out GAS pharyngitis in children was identified, but has not been validated until now."

Page 3, Abstract Objective: I suggest a modification « To identify the best clinical decision rules (CDRs) for diagnosing group A streptococcal (GAS) pharyngitis in children. A combination of symptoms could help clinicians to predict which cases of pharyngitis in children might be GAS infections. »
Answer: A modification has been done to be clearer (p3, Abstract, Objectives): "A combination of symptoms could help clinicians to exclude GAS infection in children with pharyngitis."

Conclusion « The rule of Joachim et al. could be useful for clinicians who are reluctant to use rapid diagnostic tests and should allow them avoid antibiotic treatment for children who do not have GAS pharyngitis." I think that it is not true, because very few proportion of patient (less than 30%) had had score sufficiently low to allow to not using rapid antigen test or culture.
Answer: We agree with the reviewer that the use of the best rule will avoid an antibiotic treatment for 35% of children with pharyngitis. Although it is only 35% (95%CI, 30-40), it is still a lot when considering that about 20% of the 300 millions of people in the US are under 15 and that 96/1000 [McCaig et al, JAMA 2002] receive an antibiotic for pharyngitis! It represents about 6 millions of antibiotic prescriptions that could be avoided only by the use of a good clinical decision rule in children and adolescents, and much more by the proper use of rapid diagnostic tests. To take into account the comment of the reviewer and to show the usefulness of a good clinical prediction rule in this situation, we have reformulated the 2 last sentences in the Abstract and the conclusion of the manuscript:
- Abstract (p3): "The rule of Joachim et al. could be useful for clinicians who do not use rapid diagnostic tests and should allow them avoid antibiotic treatment for the 35% of children identified by the rule as not having GAS pharyngitis."
- Conclusion (p15, lines 4-6): "The rule has only 35% Sp; but its use could avoid about 6 millions of antibiotic prescriptions in American children (< 15 y.o.) when considering that almost 20% of the 300 millions of people in the US are under 15 and that 96/1000 [2] receive an antibiotic for pharyngitis."

Reviewer: 2
Dr Carole Cummins
Senior Lecturer, School of Health and Population Sciences University of Birmingham
I have no competing interests.

I reviewed an earlier draft of this article and some of my previous points have been addressed. I said in my previous review however that the authors should make it clear that not all guidelines mandatory rapid tests, and although the authors have cited an article that makes this point, it would be worth stating that rapid tests are not recommended practice in all settings internationally, as this implies that the purpose and use to which a decision rule is put may vary. In some settings it would be used to improve diagnosis, but elsewhere might be used to reduce or replace tests. Authors could consider citing the guidelines as well as the review article. While this is perhaps not necessary for publication, it would ensure that differences in practice internationally are made clear.
Answer: We agree with this remark of the reviewer and have raised this important issue both in the introduction (p4-5): "Moreover, RDT are not recommended in practice in all settings internationally [18]." and in the discussion section (p14, lines 22-23): "It might be useful for countries were the RDT use is not recommended in current practice [18]."

My main outstanding criticism however is that I had previously suggested that databases searched using the OVID platform and via INIST should be specified or the search strategy would be incomplete and unevaluable by the reader. This has not been addressed and is an important point as it influences the assessable quality of what otherwise appears to be a high quality systematic review. It also means that updating would be difficult should anyone wish to do this. For example, was Ebase searched or the Science Citation Index? This really should be clear and would improve a useful paper considerably from the systematic review aspect.
Answer: As recommended by the reviewer, we have provided details about our search strategy. The search has been done once again during this revision to ensure its reproducibility. A flow chart has been produced (Figure 2). Changes are available in the search strategy and study selection criteria section of the Methods (p5, lines 11-23): "This systematic search and quality assessment of references was performed independently by FL and FD in august 2010. To identify eligible original articles, we searched four electronic databases: Medline via PubMed, INIST (Institute for Scientific

and Technical Information) at article@inist, database now accessible at www.Refdoc.fr, the OVID library at http://ovidsp.ovid.com/, and the Cochrane library. In the Medline search, we used the medical subject heading terms "pharyngitis" (MeSH, restricted to major topic) and "predictive value of tests" (MeSH), separated by the Boolean operator AND. Limits were set to specify "human" as the species, "all child" as the age, and year of publication from 1975 to 2010, without limits on language of publication. In the other databases only the MeSH term "pharyngitis" was used and less limits to broaden the research: in INIST via Refdoc, we used the terms "pharyngitis" and "children" from 1975 to 2010; in OVID, we used the terms "pharyngitis", "children" and "sensitivity" with limits set to specify "clinical medicine" as journal subset, and year of publication from 1975 to 2010; in the Cochrane library, we used the term "pharyngitis" alone without limits of dates."

Search dates should also be added.
Answer: It was already provided for the PubMed search and has been added for the other electronic databases. If the reviewer talks about the date when the search has been performed, it has been added in the search strategy section of the Methods (p5, lines 11-12): "This systematic search and quality assessment of studies was performed independently by FL and FD in august 2010."

Also on review methods: -A flowchart of citations might be expected in the supplementary material. Ideally text as well as MESH terms would have been used.
Answer: The flow chart has been added as recommended (Figure 2). For terms that corresponded to MESH terms (used but not mentioned indeed), the information (MESH) has been added (p5, lines 16, 17, 19): "In the Medline search, we used the medical subject heading terms "pharyngitis" (MeSH, restricted to major topic) and "predictive value of tests" (MeSH), separated by the Boolean operator AND."

There's a typo – "avec" instead of "have".
Answer: The error has been corrected in the Article summary section, p2.

Results are credible as long as more information on the databases searched is provided.
Answer: We think to have now answered to this question (see previously).

A flow chart would be desirable.
Answer: The flowchart has been added (See Figure 2).

Fig 2. Identification of clinical decision rules for the diagnosis of group A Streptococcal pharyngitis by a systematic database search.

VERSION 2 – REVIEW

REVIEWER	Robert Cohen CHI Créteil Activ 40 Avenue de Verdun 94010 Créteil Cedex Conflict of interest in the field : None
REVIEW RETURNED	16-Dec-2012

THE STUDY	The main defect of the conclusion is that the author underline the fact that some scores have a sensitivity comparable to rapid antigen test and so not underline that none has a good specificity. During an era where resistance to antibiotics is a major problem in all the world and every body know that the main driver for resistance is antibiotic

	consumption, this flaw could lead to treat with anti-infective many patients without GAS infection. This point have to be added in the abstract, the key message and the conclusion The recent guidelines on Pharyngitis from IDSA (CID october or November 2012 ist not in the reference
GENERAL COMMENTS	I suggest very few modifications Page 2 Key messages 2 “Some clinical decision rules are performing as well as some rapid diagnostic test to exclude GAS pharyngitis in children, but are not performing enough for the positive diagnosis of GAS pharyngitis. “ I think that its necessary to add « this defect could lead to over antibiotic prescription » Page 3 Abstract, Results « Among the CDRs, that of Joachim et al. had a negative likelihood ratio of 0.3 (95%CI: 0.2-0.5), resulting in a post-test probability of 13%,which leads to 3.6% false-negative rate among low-risk patients and 10.8% overall,equivalent to that of some rapid diagnostic tests » « Among the CDRs, that of Joachim et al. had a negative likelihood ratio of 0.3 (95%CI: 0.2-0.5), resulting in a post-test probability of 13%, which leads to 3.6% false-negative rate among low-risk patients and 10.8% overall, equivalent to rapid diagnostic tests in some studies » Page 3 Abstract conclusion « The rule of Joachim et al. could be useful for clinicians who do not use rapid diagnostic tests and should allow avoiding antibiotic treatment for the 35% of children identified by the rule as not having GAS pharyngitis. » I suggest to add the following sentence. « However, due to the poor specificity of the rule, by using only Joachim score, many patients who are not GAS infected and receive antibiotics » PAGE 5 New guidelines from IDA are Available in 2012 (CID November)

VERSION 2 – AUTHOR RESPONSE

Reviewer: Robert Cohen

The main defect of the conclusion is that the authors underline the fact that some scores have sensitivities comparable to rapid antigen test and so not underline that none has a good specificity. During an era where resistance to antibiotics is a major problem in all the world and everybody knows that the main driver for resistance is antibiotic consumption, this flaw could lead to treat with anti-infective many patients without GAS infection. This point has to be added in the abstract, the key message and the conclusion.

Answer: changes have been done in the abstract, key messages and conclusion as recommended (see below the answers for each of these points raised by the reviewer).

The recent guidelines on Pharyngitis from IDSA (CID october or November 2012 is not in the references
Answer: the new IDSA reference has been added as recommended (ref 12), in replacement to the old reference of the IDSA guidelines for pharyngitis (2002), and the sentence modified as follows (p4, lines 20-21): "…because the clinical features alone do not reliably discriminate between GAS and viral pharyngitis [12]."

I suggest very few modifications Page 2 Key messages 2: "Some clinical decision rules are performing as well as some rapid diagnostic test to exclude GAS pharyngitis in children, but are not performing enough for the positive diagnosis of GAS pharyngitis." I think that its necessary to add « this defect could lead to over antibiotic prescription »
Answer: changes have been done p2 in the key message n°2, as recommended, with slight changes in the key message n°3, to have a better link between key messages 2 and 3:
• Some clinical decision rules are performing as well as some rapid diagnostic test to exclude GAS pharyngitis in children, but are not performing enough for the positive diagnosis of GAS pharyngitis, which can lead to a still important antibiotic prescription level.
• Therefore, clinical decision rules could be used to focus rapid diagnostic tests to children with high risk of GAS pharyngitis to reduce the use of antibiotic.

Page 3 Abstract, Results Change the sentence : « Among the CDRs, that of Joachim et al. had a negative likelihood ratio of 0.3 (95%CI: 0.2-0.5), resulting in a post-test probability of 13%, which leads to 3.6% false-negative rate among low-risk patients and 10.8% overall, equivalent to that of some rapid diagnostic tests » to :
« Among the CDRs, that of Joachim et al. had a negative likelihood ratio of 0.3 (95%CI: 0.2-0.5), resulting in a post-test probability of 13%, which leads to 3.6% false-negative rate among low-risk patients and 10.8% overall, equivalent to rapid diagnostic tests in some studies »
Answer: Changes have been done as recommended (p3).

Page 3 Abstract conclusion « The rule of Joachim et al. could be useful for clinicians who do not use rapid diagnostic tests and should allow avoiding antibiotic treatment for the 35% of children identified by the rule as not having GAS pharyngitis. » I suggest to add the following sentence. « However, due to the poor specificity of the rule, by using only Joachim score, many patients who are not GAS infected and receive antibiotics »
Answer: changes have been done in the Abstract p3 in the conclusion section to take into account this suggestion and to limit the length of the Abstract: "Due to its poor specificity, such CDR should be used to focus rapid diagnostic tests to children with high risk of GAS pharyngitis to reduce the use of antibiotics."

PAGE 5 New guidelines from IDA are Available in 2012 (CID November)
Answer: The reference has been added as recommended (ref12, p17).